

US EPA ARCHIVE DOCUMENT

(3-16-92)

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 100-TGT
Tilt Gel Fungicide

FROM: William S. Woodrow WSW 1-13-92
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C) E 3/16/92

TO: S. Lewis / Sidney Jackson (PM 21)
Fungicide - Herbicide Branch
Registration Division (H75-05C)

APPLICANT: Ciba-Geigy Corp.
Agricultural Division
P. O. Box 18300
Greensboro, NC 27419-8300

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
<u>Propiconazole: 1-[1,2-(2,4-dichlorophenyl)-</u>	
<u>4-propyl-1,3-dioxolan-2-yl] methyl]-H-</u>	
<u>1,2,4-triazole</u>	<u>41.8</u>
<u>Inert Ingredient(s):</u>	<u>58.2</u>
Total	100.0%

BACKGROUND

Ciba-Geigy submitted acute oral, acute dermal, acute inhalation, primary eye and skin irritation, and dermal sensitization studies to support registration of Tilt Gel Fungicide (EPA Reg. No. 100-TGT). MRID NOS. used were 421170-03 through 421170-08.

RECOMMENDATION

The acute toxicity studies submitted by Ciba-Geigy are acceptable. All studies were classified Guideline Data.

LABELING

- 1) The WARNING signal word is appropriate.
- 2) The Precautionary Statements are acceptable.
- 3) Under Statements of Practical Treatment, add "^{IF NOT BREATHING, GIVE ARTIFICIAL RESPIRATION, PREFERABLY MOUTH-TO-MOUTH.} Get medical attention", to the If inhaled statement. E
- 5) Current acute toxicity profile for Tilt Gel Fungicide (EPA Reg. NO. 100 TGT):
- 4) DELETE THE PHRASE "IF IRRITATION PERSISTS" FROM THE IF ON SKIN STATEMENT OF PRACTICAL TREATMENT. E

Tilt Gel accepted acute toxicity studies continued:

Study	Classification	Tox. Category
acute oral LD ₅₀ 2745 (1912-3940) mg/kg	Guideline	III
acute dermal LD ₅₀ >2020 mg/kg	Guideline	III
acute inhalation LC ₅₀ >0.733 mg/L	Guideline	III
eye irritation opacity thru 17 days	Guideline	II
skin irritation P.I. Index 2.6	Guideline	IV
dermal sensitization not a sensitizer	Guideline	-

5) No additional acute toxicity studies are required.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Product Manager: (21) 7-18-91 Reviewer: Woodcock
 MRID No.: 421170-03 Report Date: 1-9-92
 Testing Facility: Stillmeadow, Inc. Report No. 8201-91
 Author(s): J. O. Kuhn
 Species: Rat, MSD (SD)
 Age: Young adult Observation Days (Post Exposure): (14); other ()
 Weight: M 216-276, F 180-213g
 Source: Nathan Sprague Dahlen, Houston Density 1.0406 g/ml
 Test Material: CGA-64250 41-3% GELA FL-910993 Batch 471-23, liquid
 Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Conclusion:

- LD50 (mg/kg): Males = 3565 (2408-5278) mg/kg; Females = 1852.6 (1272.7-2696.7) mg/kg; Combined = 2745 (1512.5-3940.0) mg/kg
- The estimated LD50 is _____
- Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From §81-1~~): Animals quarantined prior to test. 5M & 5F/each of 3 dose levels + 5M for one additional dose level - all fasted at least 16 hrs prior to test. Dosing by oral

Results: Intubation. Animals observed for mortality and signs of pharmacotoxicity 3 x day of treatment & 1 time daily to 14 days.

DOSAGE (Mg/kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
750 mg/kg	0/5	0/5	0/10
2000 mg/kg	0/5	3/5	3/10
3500 mg/kg	—	3/5	3/10
5050 mg/kg	4/5	5/5	9/10

Symptomology & Gross Necropsy Findings:

Gross necropsies conducted on all animals - Body weights recorded days 0, 7 & 14.
Clinical: in life - activity decrease, ataxia, bradypnea, gasping, lacrimation, nasal discharge, piloerection, polyuria.
Necropsy: discolored and discharge, diarrhea, lacrimation, nasal discharge, polyuria, salivation, liver discoloration (swarthy). Dead - Diarrhea, lacrimation, nasal discharge, polyuria, salivation, discoloration of G.I. tract, G.I. Tract distended & gas.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: (21) 7-11-91
 MRID No.: 412170-04
 Testing Laboratory: Stillmeadow, Inc.
 Author(s): V-O-Kubra
 Species: Rabbit, NZ white
 Sex: 5M & 5F
 Test Material: CGA-64250-41.3GR GEL-A PL 910993
 Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Reviewer: Woodrow M. Walter
 Report Date: 1-9-77
 Report No. 8202-91

Summary:

- LD50 (mg/kg): Males = _____; Females = _____; Combined = _____;
- The estimated LD50 is > 2020 mg/kg
- Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-2~~):

Animals acclimated prior to test. Day prior to treatment, dorsal area of rabbits clipped to hair. To expose approx. 10% body surface, 10x10cm gauze applied to animal, secured & secured, then wrapped.

Results: *some perianal itching & second to tape. "test"*

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2020 mg/kg	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

material then introduced under wrapping by means of a syringe and spread evenly over exposure den. Tape resealed. 2 rabbits exposure. Test sites raised, wiped. Observations for mortality/toxic signs made at 1/2, 3, 6 hrs and at 1 & 2 hrs to 14 days. Body weights recorded days 0, 7 & 14. Gross necropsies conducted on each animal.

Resettle

No animals died.

Clinical: In life observations included decreased defecation and diarrhea.

Necropsy: Signs of diarrhea, desiccation of stomach contents, G.I. tract distended with gas.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (S81-3)

Product Manager: (21) 9-3-91 Reviewer: W. Woodrow
 MRID No.: 421170-05 Report Date: 1-9-92
 Testing Laboratory: Stillmeadow, Inc. Report No. 8203-91
 Author(s): M.S. Albatt
 Species: Rat, HSD (SD)
 Sex: 10M + 10F Weight: M 229-300, F 215-249g
 Source: Hatten Sprague Dawley, Houston
 Test Material: CGA-64250 418 GEL-A FL-910993 Batch 471-23
 Quality Assurance (40 CFR §160.12): Yes (Q.A. & G.L.P.)

Summary:

- LC50 (mg/kg): Males = _____; Females = _____; Combined = _____
- The estimated LC50 is 20.733 mg/mL
- Mean Concentration: _____
- Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From S81-2~~): Animals were quarantined prior to testing. 5M & 5F/each of two dose levels were exposed to test material for 4 hours. Observations for mortality and or toxic signs frequently during exposure.

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
0.2482 mg/L	0/5	0/5	0/10
0.733 mg/L	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings:~~

and at least once daily thereafter for 14 days. Body weights recorded days 0, 7 & 14. A gross necropsy was performed on all animals.

The aerosol at the higher dose level was generated by pumping test material into pressure

Tox. Cat. III → 0.5 thru 5 mg/liter

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operated pressure operated Spraying Systems Co. air atomizer (4, 155) and then passing through a baffling chamber. Aerosol generated at the lower dose level generated by a pressure operated Spraying Systems Co air atomizer (4, 155) which aspirated the test material directly from its reservoir & then electrifying resulting aerosol through baffling chamber. At both dose levels, aerosol was diluted with fresh and filtered air.

Chamber concentrations determined analytically once/hour (samples collected from animal breathing zone). Analytical measurements made using Tracor Model 560 gas chromatograph.

Particle size determined & during each exposure (samples collected from breathing zones), using an Anderson Cascade Impactor, at 28.3 L/min. for 3-10 min. MMAD calculated.

Results:

1) Chamber concentration (average of 8 samples each dose)
high dose = 0.733 mg/L Nominal 42.9 mg/L
 (analytical)

low dose = 0.2482 mg/L Nominal 35.9 mg/L
 (analytical)

NOTE approximately a 3 fold difference in dosage levels (analytical)

Results (Cont.)

2) Particle Size Distribution
Low dose

1 hr sample: μ

Cum. %

stage	size range	μ in size range	← size range
4	2.1-3.3	17.68	20.49
5	1.1-2.1	12.08	8.40
6	0.7-1.1	2.27	6.12
7	0.4-0.7	0.35	5.77

MMAD 3.318 μ , GSD = 2.469

2 hr sample

4	2.1-3.3	17.56	21.55
5	1.1-2.1	12.57	8.98
6	0.7-1.1	3.19	5.78
7	0.4-0.7	0.97	4.79

High Dose

MMAD 2.245 μ , GSD 2.386

1 $\frac{1}{4}$ hr sample

4	2.1-3.3	28.47	38.26
5	1.1-2.1	35.30	2.96
6	0.7-1.1	0.45	2.50
7	0.4-0.7	0.91	1.59

3 $\frac{1}{4}$ hr sample

MMAD 2.532 μ , GSD = 1.825

4	2.1-3.3	21.17	42.41
5	1.1-2.1	39.44	2.26
6	0.7-1.1	0.85	2.11
7	0.4-0.7	0.52	1.58

MMAD 2.502 μ , GSD = 1.816

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Clinical symptoms: In life observations included
 activity decrease, corneal opacity, nasal discharge,
 prostration, polyuria, ptosis, respiratory gasps and
 salivation.

Gross necropsy: No gross abnormalities -

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: (21) 3-15-91 Reviewer: W. Meadows
 MRID No.: 421170-06 Report Date: 1-13-92
 Testing Laboratory: Stillmeadow, Inc. Report No. 7820-91
 Author(s): J. O. Kulin
 Species: Rabbit, NZ White
 Sex: 3M & 6F Weight: not given
 Source: Ray Nichols Rabbitry, TX
 Dosage: 0.1 ml
 Test Material: CGA-64250 GEL-PAD FL-910065, liquid
 Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary:

Tox. Category: II Classification: Guideline

Procedure (~~Deviation From §81-4~~): Animals acclimated at least one week. Both eyes each animal examined 24 hrs prior to test, using a 2% Fluorescein (for defects). 0.1 ml (undiluted) placed in conjunctival sac right eye each animal. Lids held together 1 sec. Three eyes washed, remainder unwashed. Treated eyes examined & scored for irritation (Deaize),
 Observations

Unwashed eyes only (6 eyes)	(number "positive"/number tested)										
	Hour	Days									
		1	1	2	3	4	7	10	14	17	21
Cornea Opacity →	0/6	6/6	6/6	6/6	6/6	3/6	1/6	1/6	1/6	0/6	0/6
Iris	2/6	2/6	1/6	1/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	6/6	6/6	6/6	6/6	6/6	6/6	3/6	1/6	1/6	1/6	1/6
Chemosis	6/6	6/6	6/6	5/6	3/6	0/6	0/6	0/6	0/6	0/6	0/6
Discharge	6/6	6/6	6/6	6/6	6/6	1/6	1/6	1/6	1/6	1/6	0/6

Comments: at 1, 2, 4, 14, 17 hrs, and at 4, 7, 10, 14, 17 and 21 days post treatment. Corneal involvement absent by 21 days, conjunctival redness persisting through 21 days (1/6 animals); however, according to the guidelines, 1-redness is not to be considered a positive effect.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (21) 7-9-91
 MRID No.: 421170-07
 Testing Laboratory: Stillmeadow, Inc.
 Author(s): V.D. Kuhn
 Species: Rabbit
 Age: 3 to 6 months
 Sex: 3M + 3F
 Weight: Not given
 Dosage:

Reviewer: Woodrow M. Waller
 Report Date: 1-13-92
 Report No.: 8204-91

Test Material: CGA-04250 4L3 GEL-A, PL-910993, liquid
 Quality Assurance (40 CFR §160.12): yes (P.A. & G.L.P.)

Summary:

The Primary Irritation Index = 2.6
 Toxicity Category: IV
 Classification: Guideline

Procedure (~~Deviations From §81-5~~): Animals acclimated at least 1 week prior to test. Day before test, dorsal area clipped free of hair (8x8cm) = 1 intact site. Each site (6 animals) treated with 0.5ml undiluted test material "by introducing beneath gauze patches - 2.5x2.5cm". Patches secured with tape. Entire trunk wrapped with semi-occlusive material, secured to tape. Front lower skin exposed. Wrappings, patches removed, sites wiped, scored for erythema/edema @ 3, 24, 48, 72 hours and Days 7, 10, 14, 17 and 21. Draize system.

Results: Primary Irritation Scores; 6 animals =

P.I. (overal)	2.75
intact	13.00
= 2.6	3.00
	3.25
	2.25
	3.25

Special Comments:

During serious rashes -
 0.51-3.0 rating "Mildly irritating"

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (21) 8-1-91
MRID No.: 421170-08
Testing Laboratory: stillmeadow
Author(s): J.O. Kubin
Species: Guinea Pig, Hartley
Sex: 12 M & 12 F
Source: Harlan Sprague Dawley, Houston, TX
Test Material: CGA 164250 41.8% GEL-A FL-910993 Batch 471-23, liquid
Positive Control Material: 1-chloro, 2,4-dinitrobenzene (DNBC)
Quality Assurance (40 CFR §160.12): 405 (Q.A. & G.L.P.)

Reviewer: M. ~~Walden~~ Woodrow
Report Date: 1-13-92
Report No: 8205-91

Method: Modified Beechler

Summary:

1. This product is / is not a dermal sensitizer.
2. Classification: Guideline

Procedure (~~Deviation From §81-6~~): Animals acclimated at least 5

days. A pre-test screening test to determine a maximum, non-irritating concentration to use for the main study. Four animals used for this purpose.

Results: 2 males and 2 females. 5, 20, 50, and 100% test material was assessed. 0.5ml doses were applied - 2 concentrations per animal. Doses covered with patches, backs wrapped with polyethylene film. 6 hour exposure.

Based on this range finding study,

Induction:

Based on the range finding study, 50% test material v/v solution in 95% ethanol was used for induction. 20-0 to v/v solution in 95% ethanol used to challenge animals. 5M & 5F animals (Group 1) remained untreated until challenge. 5M & 5F were treated once weekly to total three inducing treatments, using 0.5ml of 50% v/v solution of test material in 95% ethanol. Induced animals treated by introducing test material beneath 3.8 x 5cm patch gauze pad secured with tape (known as a Coverlet adhesive dressing) (left front quadrant). Entire trunks of animal

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wrapped with clear polyethylene film secured with tape.
 (24 hrs prior to treatment; dorsal area of each animal
 clipped free of hair). Following treatment, each animal placed
 in a restrainer for 6 hours. Wrappings, patches removed.
 Animals induced weekly, using same test sites.

Two weeks following last induction application, animals
 challenged in same manner as before, on the right rear
 quadrant using 20% v/v solution of T.M. in 95% ETOH.

Observations for skin reactions made @ 24 hours
 post patch removal. Also, observations for skin reactions
 made approx. 48 hrs following patch removal, after
 induction treatments 1 and 3, and after the challenge.

SM & SP challenged simultaneously with the induced
 animals (challenge only for these naive animals)

Application and sewing procedures same (Naive animals
 also challenged with the 20% preparation).

Decided from tester's report:

treatment	Day	Group	Original test site	Virgin test site (challenge)
initial	1	naive control	NA	NA
challenge	29	naive control	NA	0.0
initial	1	Test	0.2	NA
challenge	29	Test	NA	0.0

NA = not applicable

Unquote -

Discussion of tubercular information presented above:

- 1) Note that the naive animals challenged (only) with 20% test material exhibited 0.00 scoring.
- 2) For the test animals, the 0.2 represents the average induction score - induced to 50% test mat.
- 3) Note that the induced test site - was not challenged.
- 4) The naive test site on the induced animals exhibited no reaction, scoring was 0.00

Conclusion: The test material did not sensitize guinea pig.

Positive Controls: 5M & 5F induced 3x at weekly intervals (in same manner as test animals), and challenged two weeks following final induction. 5M & 5F naive control animals challenged only. (0.6% W/V in 9.5% BTOR). DNBC. The test portion of materials and methods states "DNBC tested periodically to confirm sensitivity of guinea pig."

Tox Chem. No.

File Last Updated

Current date

323EE Propiconazole

1-13-92

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
acute oral LD50, Rat. Stillmeadow, Inc. #8201-91	Propiconazole Tilt Gel	421170 -03	LD50 = 2745 (912-3940) mg/kg	III	Guide line
acute dermal LD50, Rabbit Stillmeadow, Inc. #8202-91	"	421170 -04	LD50 > 2020 mg/kg	III	Guide line
acute inhalation LC50, Rat Stillmeadow, Inc.	"	421170 -05	LC50 > 0.733 mg/L	III	Guide line
#8203-91 Eye Irritation, Rabbit Stillmeadow, Inc. #7820-91	"	421170 -06	1/6 rabbits 1.0 @ 21 days (1.0 not consid- ered positive	II	Guide- line
skin irritation, Rabbit Stillmeadow, Inc. #8204-91	"	421170 -07	P.I. Index 2.6 0.51-3.0 = Tok. IV	IV	Guide- line
dermal sensitization, guinea pig Stillmeadow, Inc. #8205-91	"	421170 -08	Not a dermal sensitizer	-	Guide- line

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